IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/559,995	Confirmation No. 4575
Applicant	:	Kanikanti et al.	
Filed	:	August 7, 2007	
Title	:	Tablets containing enrofloxacin and flavoring agents and/or flavors	
Group Art Unit	:	1619	
Examiner	:	Raymond Yeager	

VIA EFS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF VENKATA-RANGARAO KANIKANTI
UNDER 37 C.F.R. §1.132

Dr. Venkata-Rangarao Kanikanti declares and states as follows:

1. I received a Master in Pharmacy degree from Mysore University, in India. Thereafter, I received a Doctorate in Pharmacy from the University of Panjab in India.

2. From January 1989 to date, I have been employed by Bayer. My present position is Laboratory Manager.

3. Under my direction and control, a study to compare the tablet of the present invention (uncoated tablet that includes enrofloxacin, lactose, microcrystalline cellulose, and other excipients, Batch No. 1165 on the graph attached) vs. a tablet having standard ingredients (exchange of microcrystalline cellulose and lactose for maize starch – all other ingredients are the same, Batch No. 1164 on the graph attached) was conducted. The exact formulation for the tablets tested is attached in

table form herewith. Maize starch is a common filler for tablets. In addition, it is considered to have an advantage over lactose in that it also acts as a disintegrant. The tablets were compared for their crushing strength and friability at different compression forces.

4. For the tablet of the present invention, that includes microcrystalline cellulose and lactose, has a considerably higher crushing strength and lower friability than the maize starch tablet.

5. The tablets were tested according to the USP friability test which is used to determine the abrasion resistance (= friability) of tablets. The abrasion is required to be below 1% by the United States Pharmacopeia (See USP 23, page 1981, attached herewith for testing method and range).

6. For the tablet of the present invention, no abrasion was detected. For the maize tablets made with a compression force of 10 and 20 kN, they broke in the abrasion test. For the maize starch tablets made with 30 kN, they have an abrasion of 7.66%, which is unacceptable (higher than 1% allowed).

7. As can be observed based on these results, the significant difference between crushing strength and friability is not anticipated based on changing maize starch, a common filler, to microcrystalline cellulose and lactose. It is surprising that a combination of microcrystalline cellulose and lactose made the tablet perform so well.

8. The applicant further declares that all statements made herein are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false

statements may jeopardize the validity of the application or any patent issuing therefrom.

K. V. Rangarao Kanikanti

Dr. Venkata-Rangarao Kanikanti

26/APRIL/2012

Date

1995

USP 23
NF 18

THE UNITED STATES PHARMACOPEIA
THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 8–10, 1990. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 1995

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

...chnology and have knowledge of industrial sterilization, aseptic processing, and the statistical concepts involved in sampling. These individuals should be knowledgeable also concerning the environmental control program in the test facility to assure that the microbiological quality of the air and critical work surfaces is consistently acceptable.

Quality control sterility tests (either according to the official compendial test or modified tests) may be carried out in two separate stages in order to rule out false positive results. *First Stage*: Regardless of the sampling plan used, if no evidence of microbial growth is found, the results of the test may be taken as indicative evidence of intrinsic contamination of the lot.

If microbial growth is found, proceed to the *Second Stage* unless the *First Stage* test must be invalidated. Evidence for invalidating a *First Stage* test in order to repeat it as a *Second Stage* test may be obtained from a review of the testing environment and the relevant records thereto. Finding of microbial growth in negative controls need not be considered the sole grounds for invalidating a *First Stage* test. When proceeding to the *Second Stage*, particularly where depending on the results of the test of the release, concurrently, initiate and document a complete review of all applicable production and control records. In this review consideration should be paid to the following: (1) a check of monitoring records of the validated sterilization cycle applicable to the product; (2) sterility test history relating to the parental product for both finished and in-process samples, as well as sterilization records of supporting equipment, containers/closures, and sterile components, if any; (3) environmental control data, including those obtained from media fills, exposure plates, settling records, any sanitization records and microbial monitoring records of operators, gowns, gloves, and garbing practices.

Failing any lead from the above review, the current microbial profile of the product should be checked against the known historical profile for product sterility. Records should be checked occasionally for any changes in source of product components and/or in processing procedures that might be contributory. Depending on the findings, and in extreme cases, consideration may have to be given to revalidation of the total manufacturing process. For the *Second Stage* test it may possible to specify a particular number of specimens to be taken for testing. It is usual to select double the number specified for the *First Stage* under *Sterility Test* (71), or other reasonable number. The minimum volumes must be each specimen, the media, and the incubation periods for the same as those indicated for the *First Stage*.

If no microbial growth is found in the *Second Stage*, and the documented review of appropriate records and the indicated product investigation does not support the possibility of intrinsic contamination, the lot may meet the requirements of a test for sterility. If growth is found, the lot fails to meet the requirements of the test. As was indicated for the *First Stage* test, the *Second Stage* test may similarly be invalidated with appropriate evidence, and, if so done, repeated as a *Second Stage* test.

(1216) TABLET FRIABILITY

This informational chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure described in this chapter is generally applicable to most compressed tablets, and supplements other physical strength measurements, such as tablet crushing strength.

Use a 285-mm (11.3) drum, about 39 mm in depth, of transparent synthetic polymer with polished internal surfaces, and with a mold to static build-up (see Figure). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at approximately 25 rpm. Thus, at each turn the tablets roll or slide and fall about 130 mm onto the drum and on each other.

Tablet Friability Apparatus

For tablets weighing up to 650 mg each, use a 6- to 6.5-g sample. A minimum number of 20 tablets should be used in any test; however, for tablets weighing over 650 mg each, a 10-tablet sample is sufficient. Place the tablets on a No. 10 sieve and remove any loose dust with the aid of air pressure or a soft brush. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, reweigh any broken tablets, and weigh.

Generally, the test is run once. If the results are doubtful or if the weight loss is greater than 1%, the test should be repeated twice and the mean of the three tests determined. A maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable for most products. In the case of new formulations, an initial weight loss of 0.8% would be permitted until sufficient packaging data are obtained to extend the limit to 1%.

For tablets having a diameter of 13 mm or greater, if frequent, irregular tumbling causing reproducibility problems is observed, adjust the drum so that its axis forms a 10° angle with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned, and these tablets normally require special packaging. In the case of hygroscopic tablets, care must be taken to perform the test quickly enough to prevent weight gain, and all weighing should be done in a closed weighing dish.

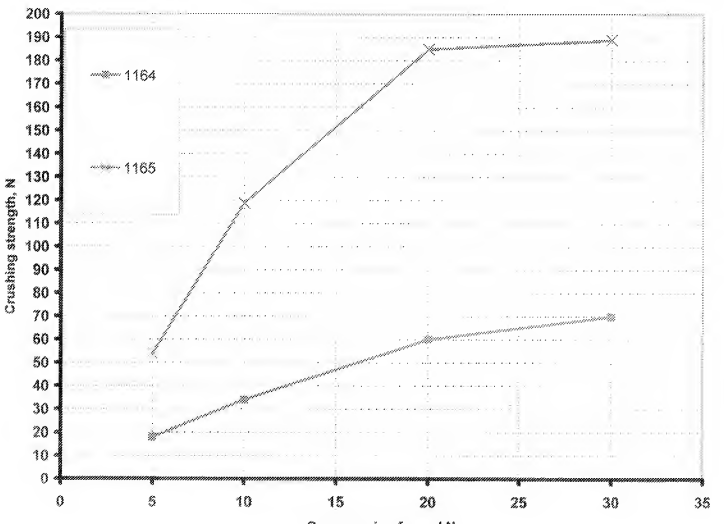
A drum with dual scooping supports for the running of two samples at one time is also available.

(1221) TEASPOON

For household purposes, an American Standard Teaspoon has been established by the American National Standards Institute[1] as containing 4.93 ± 0.24 mL. In view of the almost universal practice of employing teaspoons ordinarily available in the household for the administration of medicine, the teaspoon may be regarded as representing 5 mL. Preparations intended for administration by teaspoon should be formulated on the basis of dosage in 5-mL units. Any dropper, syringe, medicine cup, spoon, or other device used to administer liquids should deliver 5 mL whenever a teaspoon calibration is indicated. Under ideal conditions of use, the volume error incurred in measuring liquids for individual dose administration by means of such calibrated devices should be not greater than 10% of the indicated amount.

The apparatus meeting these specifications is available from scientific supply houses such as VanNuys Instruments, Inc., 36 Meadow Road, Edison, NJ 08820, or from Erweka Instruments, 58 Quirk Road, Milford, CT 06460.

[1] American National Standards Institute, 1430 Broadway, New York, NY 10018.


Crushing strength, N
Compression force, kN
1164
1165
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
0
5
10
15
20
25
30
35

Attachment A

The composition of the two formulations is as follows:

	1164 (% w/w)	**1165** (% w/w)
Enrofloxacin	20	20
Lactose monohydrate	-----	35
Microcrystalline cellulose	-------	10
Maize starch	52	7
Povidone 25	5	5
Artificial beef flavor	20	20
Colloidal silicon dioxide	2.0	2.0
Magnesium stearate	1.0	1.0

The ingredients are mixed well and passed through a 1 mm screen manually and then compressed into tablets weighing 750 mg using tools of oblong shape (18 mm length and 8 mm width with one score). The compression force was varied as shown in the diagram attached. The samples collected at each compression were tested for tablet hardness and friability as described by the USP.

Determination of the crushing strength:
The tablets are placed between the jaws of the hardness tester (Machine type: Schleuniger 6D hardness tester) in such a way that the tip of the capsule shape will be in contact with the jaws when the jaws move. The force in Newtons required to crush the tablets is noted. This is a routine procedure done by the skilled person in the art for determining the tablet hardness with Schleuniger hardness tester.